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Docket No.: 532512000401
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Gregory M. LANZA et al.

Application No.: 10/620,725

Filed: July 15, 2003

For: LIGAND-TARGETED EMULSIONS
CARRYING BIOACTIVE AGENTS

Confirmation No.: 1157

Art Unit: 1615

Examiner: David L. Vanik, Ph. D.

DECLARATION OF GREGORY M. LANZA

Commissioner for Patents
P.O. Box 1450
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Dear Sir:

I, Gregory M. Lanza, declare as follows:

1. I am a co-inventor of the subject matter described in the above-referenced application. I have been working with targeted fluorocarbon nanoparticles as drug delivery carriers and as imaging agents for over a decade. A copy of my *curriculum vitae* is attached.

2. I prepared the compositions of doxorubicin and paclitaxel described in Examples 1-2 and 4 of the present application, as well as a similar composition containing rapamycin. In all cases, the drug is mixed with initial ingredients in a solvent such as chloroform and evaporated to a film prior to forming the nanoparticles, rather than added at a later time in the preparation.

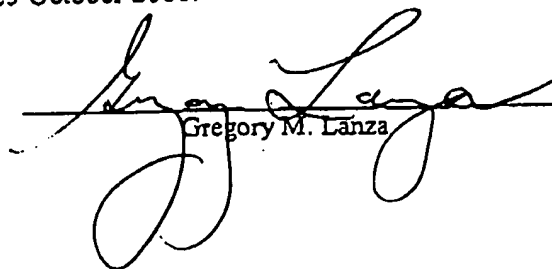
3. Doxorubicin, supplied as the hydrochloride, is highly water-soluble. Doxorubicin-loaded nanoparticles, where the doxorubicin is not incorporated into the solvent film prior to preparation of the particles, is either not incorporated into, or rapidly released out of, the lipid/surfactant layer.

4. Paclitaxel is very insoluble in water and adding the drug to water leads to crystalline precipitation. If ethanol is added, the emulsion is cracked or destroyed. However, following the procedure of the present application - i.e. mixing in solvent with ingredients of the lipid/surfactant layer and evaporating prior to forming the nanoparticles, it can be successfully included and retained in the lipid/surfactant layer.

5. I have done similar experiments with rapamycin, which is also poorly soluble in water. By following the procedures outlined in the present application, stable loading of the drug in the lipid/surfactant layer is achieved.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at San Diego, California, on 25 October 2006.


Gregory M. Lanza



Gregory M. Lanza, M.D., Ph.D.
007-54-0672

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Personal Information:

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Present Position:

Associate Professor of Medicine
Adjunct Associate Professor of Biomedical Engineering

Education:

1975: Bachelor of Arts
Colby College
Waterville, Maine 04901

1978: Masters of Science
Department of Poultry Science
University of Georgia
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1981: Doctor of Philosophy
Department of Poultry Science
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1992: Doctor of Medicine
Northwestern University Medical School
Chicago, Illinois 60611

Academic Positions/Employment:

9/04-Present	Adjunct Associate Professor of Biomedical Engineering Washington University Medical Center St. Louis, Missouri 63110
9/04-Present	Associate Professor of Medicine/Cardiology Washington University Medical Center St. Louis, Missouri 63110
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7/99-9/2004	Assistant Professor of Medicine/Cardiology Washington University Medical Center St. Louis, Missouri 63110
7/96-6/99:	Research Instructor of Medicine Washington University Medical Center St. Louis, Missouri 63110
6/94-6/99:	Cardiology Fellowship Program Barnes-Jewish Hospital Washington University Medical Center St. Louis, Missouri 63110
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8/88-6/92:	Northwestern University Medical School 303 Chicago Avenue Chicago, Illinois
6/81-8/88:	Animal Sciences Division Monsanto Company 700 Chesterfield Parkway St. Louis, Missouri
1985-1988:	Product Biology Research Manager Budget: \$2.9 Million/yr; Responsibility: Establish and direct a preclinical product development research program for dairy use of recombinant bovine somatotropin in support of US and ex-US regulatory approvals. The position was responsible for supporting the development and optimization of the product, designing, conducting and analyzing target and model animal pharmacodynamic

(efficacy and physiology), pharmacokinetic, safety (toxicology, clinical and anatomical pathology) and metabolism residue studies. Statistics and Quality Assurance groups were also created and managed between 1983 and 1988.

1984-1985: Senior Research Group Leader

1983-1984: Research Specialist

1981-1983: Senior Research Biologist

1976-1981: Department of Poultry Science
University of Georgia
Athens, Georgia 30602

Research at the MS and PhD levels focused on biochemically quantifying resistance/susceptibility of *Gallus domesticus* to aflatoxicosis and developing corresponding genetic selection programs.

1978: International Research in Greece

Responsibility: Provide consultation and conduct research in Greek agricultural environment concerning the incidence of tibial dyschondroplasia, an issue of international litigation between Voktas, Inc. and Central Soya, Inc. (P.I. Drs. Leo Jensen and Roland Leach).

Medical Licensure and Board Certification:

Diplomat of the National Board of Medical Examiners, Parts I, II and III
Missouri Medical License: #101080 (1993)
Diplomat of American Board of Internal Medicine, 11/95
Diplomat of American Board of Internal Medicine, Cardiology, 11/99
American Society of Echocardiography, Specialty Certification in Echocardiography, 6/1999

Honors and Awards:

Phi Kappa Phi Honor Society
Gamma Sigma Delta Agricultural Honor Society
Hubbard Farms Charitable Foundation Scholarship
Poultry Science Association Graduate Student Award
Northwestern University Medical Student Research Grant
NIH Research Festival for Outstanding PGY1 Researchers.
American Heart Association Fellowship, Missouri Affiliate (1995-1997)
Bristol-Myers Squibb Fellowship Award (1997)
Bracco Diagnostics Inc./Society for Cardiac Angiography and Interventions Fellowship (1998)
1998 ACC/Littmann Scholarship Award
American Heart Association, Missouri Affiliate – Beginning Grant (1999-2001)

American College of Cardiology, Searle Career Development Award (2000)
Barnes-Jewish Hospital Research Foundation Award (1999-2001)
NCI Unconventional Innovation Program Awards (2000-2003, 2002-2005, 2003-2006)
NHLBI RO1 (2004-2008)

Professional Societies and Organizations:

Acoustic Society of America
American Association for the Advancement of Science
American Medical Association
Missouri Board of Healing Arts
American Heart Association
American College of Cardiologists
Society of Cardiovascular Magnetic Resonance
International Society for Magnetic Resonance in Medicine
American Society of Echocardiology
Society for Molecular Imaging

Research Support:

American Heart Association Fellowship, Missouri Affiliate (1995-1997):
Principal Investigator
Barnes Jewish Hospital Foundation (1996-1997): \$50,000, Principal Investigator
Bracco Diagnostics Inc./Society for Cardiac Angiography and Interventions
Fellowship (1998-1999): \$25,000, Principal Investigator
American Heart Association, Missouri Affiliate – Beginning Grant (1999-2000):
\$35,000/yr, Principal Investigator
Barnes Jewish Hospital Foundation (1999-2000): \$50,000, Principal Investigator
American College of Cardiology Searle Award in Cardiovascular Disease (2000)
\$40,000, Principal Investigator
National Cancer Institute (2000-2003): \$2,092,153, Principal Investigator
Barnes Jewish Hospital Foundation (2000-2001): \$40,000, Principal Investigator
National Cancer Institute (2002-2005): \$2,782,905, Principal Investigator
National cancer Institute (2003-2006): \$5,097,055, Principal Investigator
National Health Lung and Blood Institute (2004-2008): ~\$1,000,000, Principle Investigator

Issued US Patents (> 25 Pending):

1. DeGeeter M J, Lanza GM, Vineyard BD. Composition and method for improving feed utilization or tissue production in animals. 10/21/1986, Monsanto Company. US Pat. No. 4,618,604. EEC Pat No. EP00139624B1, 04/15/1987.
2. DeGeeter M J, Lanza GM. Method for improved bovine milk production. 08/03/1983, Monsanto Company. EEC Pat No. EP00085036A1.
3. Lanza GM, Alkan MH, Klegerman ME, Vonesh MJ, McPherson DD. Acoustically reflective liposomes and methods to make and use the same. 03/18/1997, Northwestern University, US Pat. No:5,612057.

4. **Lanza GM, Wickline SA.** Avidin-Biotin conjugated emulsions as a site specific binding system. 11/25/1997, Barnes-Jewish Hospital. US Pat. No. 5,690,907.
5. **Lanza GM, Wickline SA.** Method of MRI using avidin-biotin conjugated emulsions as a site specific binding system. 07/14/1998, Barnes-Jewish Hospital. US Pat No. 5,780,010.
6. **Lanza GM, Alkan-Onyuksel MH, Klegerman ME, Vonesh MJ, McPherson DD, Kane BJ, Murer SE.** Acoustically reflective liposomes and methods to make and use the same. 01/12/1999, Northwestern University. US Pat No. 5,858,399.
7. **Lanza GM, Wickline SA.** Site specific binding system, imaging compositions and methods. 11/23/1999, Barnes-Jewish Hospital. US Pat No. 5,989,520.
8. **Lanza GM, Wickline SA.** Site specific binding system, nuclear imaging compositions and methods. 09/28/1999, Barnes-Jewish Hospital. US Pat No. 5,958,371.
9. **Lanza GM, Wickline SA.** Site specific binding system, imaging compositions and methods. 11/23/1999, Barnes-Jewish Hospital. US Pat No. 6,548,046.
10. **Lanza GM, Wickline SA.** Ligand-targeted emulsions carrying bioactive agents. October 28, 2000. US Patent 6,676,963.

Bibliography (abstracts not included):

1. **Lanza GM, Washburn KW, Wyatt RD, Edwards HM Jr.** Depressed Fe-59 absorption due to dietary aflatoxin. *Poultry Sci* 1979; 58:1439-1444.
2. **Lanza GM, Washburn KW, Wyatt RD.** Variation with age in response of broilers to aflatoxin. *Poultry Sci* 1980; 59: 282-288.
3. **Stewart RG, Wyatt RD, Lanza GM, Edwards HM Jr, Ruff MD.** Physiological effects of Gentian violet on broiler chickens. *Poultry Sci* 1980; 59: 234- 239.
4. **Lanza GM, Washburn KW, Wyatt RD.** Strain variation in hematological response of broilers to dietary aflatoxin. *Poultry Sci* 1980; 59: 2686-2691.
5. **Washburn KW, Maeda Y, Lanza GM.** Protein polymorphisms in a randombred chicken population. *Anim Blood Groups and Biochem Gen* 1980; 11: 261-269.
6. **Lanza GM, Washburn KW, Wyatt RD.** Time-course analysis of chick (*Gallus domesticus*) response during aflatoxicosis. *Toxicon* 1980; 19: 563-566.
7. **Lanza GM, Washburn KW, Wyatt RD.** Effect of linoleic acid on broilers to graded levels of aflatoxin. *Arch Geflugelk* 1981; 45: 206-211.

8. **Lanza GM**, Washburn KW, Wyatt RD, Edwards HM Jr. Strain variation in Fe-59 absorption during aflatoxicosis. *Poultry Sci* 1981; 60: 500-504.
9. **Lanza GM**, Washburn KW, Wyatt RD, Marks HL. Genetic variation of physiological response to aflatoxin in *Gallus domesticus*. *Theor and Appl Genet* 1981; 63: 207-212.
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11. **Lanza GM**, Washburn KW, Wyatt RD. The effect of dietary aflatoxin concentration on the assessment of genetic variability of response in a randombred population. *Genetics* 1983; 104: 123-131.
12. Renwick GM, Washburn KW, **Lanza GM**. Genetic variability in growth response to cold brooding temperature. *Poultry Sci* 1985; 64: 785-788.
13. Washburn KW, Wyatt RD, Potts PL, **Lanza GM**. Effects and mechanism of aflatoxin variation in shell strength. *Poultry Sci* 1985; 64: 1302-1305.
14. Bauman DE, Eppard PJ, DeGeeter MJ, **Lanza GM**. Responses of high producing dairy cows to long-term treatment with pituitary somatotropin and recombinant somatotropin. *J Dairy Sci* 1985; 68: 1352-1362.
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17. **Lanza GM**, Zabalgaitia-Reyes M, Frazin L, Meyers SN, Spitzzeri CL, Vonesh MJ, Mehlman DJ, Talano JV, McPherson DD. Plaque and structural characteristics of the descending thoracic aorta using transesophageal echocardiography. *J Am Soc Echo* 1991; 4: 19-28.
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- dairy cows to high doses of a sustained release bovine somatotropin administered during two lactations. II. Health and Reproduction. *J Dairy Sci* 1992; 75: 111-23.
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 22. Eppard PJ, Bentle LA, Violand BN, Ganguli S, Hintz RL, Kung L Jr, Krivi GG, **Lanza GM**. Comparison of the galactopoietic response to pituitary-derived and recombinant-derived variants of bovine growth hormone. *J Endocrinology* 1992; 132: 47-56.
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 30. **Lanza GM**, Scott MJ, Davison G, Hall CS, Christy DH, Miller JG, Wickline SA. Angiotensin II Receptor Blockade in Syrian Hamster (T0-2) Cardiomyopathy

does not affect microscopic cardiac material properties: implications for mechanisms of tissue remodeling. *Cardiovasc Drug Ther* 1997; 11: 521- 529.

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46. Yu X, Song S-K, Chen J, Scott MJ, Fuhrhop RJ, Hall CS, Gaffney PJ, Wickline SA, **Lanza GM**. High-resolution MRI characterization of human thrombus using a novel fibrin-targeted paramagnetic nanoparticle contrast agent. *Magn Reson Med* 2000; 44: 867-872.
47. Hall CS, Marsh JN, Scott MJ, Gaffney PJ, Wickline SA, **Lanza GM**. Time evolution of enhanced ultrasonic reflection using a fibrin-targeted nanoparticle contrast agent. *J Acoust Soc Am* 2000; 108: 3049-3057.
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51. Hall CS, Marsh JN, Scott MJ, Gaffney PJ, Wickline SA, **Lanza GM**. Temperature dependence of ultrasonic enhancement with a site-targeted contrast agent. *J Acous. Soc Am* 2001; 110: 1677-1684.

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Abstracts from Technical Meetings:

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oncologic and cardiovascular diseases. Contrast Media Research Symposium, San Diego, CA, October, 2003 (In Press)

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Chapters:

1. **Lanza GM**, Wallace KD, Miller JG, Wickline SA. Development of a novel site targeted ultrasonic contrast agent. In: Advances in Echo Imaging Using Contrast Enhancement. N.C. Nanda, R. Schlieff, and G.G. Goldberg, editors. Kluwer Academic Publishers, Norwell, MA. 1997, pp. 655-667.
2. Wickline SA, Miller J, **Lanza G**. Quantitative ultrasonic tissue characterization with intravascular and transcutaneous ultrasound. In: Non-invasive Imaging of Atherosclerosis. M. Mercuri, D.D. McPherson, H. Bassiouny, S. Glagov, editors. Kluwer Academic Publishers, Norwell, MA. 1998, pp 169-188.
3. **Lanza GM**. Wickline SA. Targeted ultrasonic contrast agents for molecular imaging and therapy. In: Progress in Cardiovascular Diseases. M. Lesch and E H. Sonnenblick, editors. W. B. Saunders, Philadelphia, PA. 2000, pp 13-31.
4. **Lanza GM**, Caruthers SD, Wickline SA: Molecular Imaging. In *MRI of the Cardiovascular System*, ed Lardo, Fayad, Chronos and Fuster. Martin Dunitz Ltd. London (In press)
5. Tillman C, Winter PW, Wickline SA, **Lanza GM**: Nanoparticle formulations for cardiac magnetic resonance imaging. *Expert Review of Cardiovascular Therapy* (In press)
6. Winter PM, Caruthers SD, Wickline SA, **Lanza GM**: Nanotechnologies for Cellular and Molecular Imaging by MRI, In "Nanofabrication Towards

biomedical Applications" (C Kumar, J Hormes, C Leuschner Eds.), Wiley-VCH (in review)

7. Targeted MRI Contrast Agents In Magnetic Resonance Imaging: Methods and Biological Applications SD Caruthers, PM. Winter, SA. Wickline and GM. Lanza. (In Press)

Invited Presentations (since 1997)

1. Invited Speaker: Contrast Media Research, Kyoto, Japan, 5/97 - Enhanced detection of thrombi with a novel fibrin targeted magnetic resonance imaging agent.
2. Invited Speaker: Nycomed Imaging, Inc, Oslo, Norway, 6/97 - Review of targeted contrast applications for ultrasonic imaging.
3. Invited Speaker: NIH Seminar, Washington, DC, 9/97 - A novel targeted contrast agent for ultrasonic and magnetic resonance imaging.
4. Invited Speaker: Abbott, Inc, Chicago, IL, 10/97 - Review of targeted contrast technology for ultrasonic and MRI imaging.
5. Invited Speaker: Imclone Systems, Inc, Chicago, IL, 2/98 - Review of targeted contrast technology for ultrasonic and MRI imaging.
6. Invited Speaker: Acoustic Society of America, Seattle, WA 5/98 - Targeted acoustic contrast agents: new opportunities for ultrasound in medical diagnosis and therapy.
7. Invited Speaker: Abbott, Inc, Chicago, IL, 12/99- Updated review of targeted contrast technology for ultrasonic and MRI imaging.
8. Invited Speaker: WU Biochemical Engineering Seminar 12/99 - Molecular Imaging with Ligand-Targeted Immunoemulsions.
9. Invited Speaker: Schering AG, Inc, Berlin, Germany 5/2000- Updated review of targeted contrast technology for ultrasonic and MRI imaging.
10. Invited Speaker: Allerton Conference, Acoustic Contrast Agents, Allerton, Illinois 6/2000- Targeted acoustic contrast agents: new opportunities for ultrasound in medical diagnosis and therapy.
11. Invited Speaker: FMC Technology Review –2000, Princeton, NJ 9/2000 – Angiogenesis and Wound Healing
12. Invited Speaker: Imaging in 2020 (NCI) – 9/2001 – “Molecular Imaging and Targeted Drug Delivery with a Novel Perfluorocarbon Nanoparticle”
13. Invited Speaker: CMR 2001, 10/2001 Capri, Italy – “Molecular Imaging and Targeted Drug Delivery with a Novel, Ligand-Directed Paramagnetic Nanoparticle Technology”

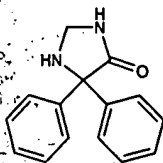
14. Invited Speaker: International Society for BioMEMS and Biomedical Nanotechnology 9/2001, Columbus, OH – “Magnetic Resonance Molecular Imaging and Targeted Drug Delivery with Site-specific Nanoparticles”
15. Invited Speaker: NCI Unconventional Innovative Projects Program – Washington, DC - 2/2002 – “Molecular Imaging and Local Drug Delivery With a Novel AvB3-Targeted Nanoparticle Emulsion for Noninvasive Detection and Treatment of Cancer”
16. Invited Speaker: Vulnerable Plaque Symposium 3/2002 Atlanta, GA “MR Imaging of Fibrin to Detect Plaque Mural Thrombi “
17. Invited Speaker: Saint Louis University Cardiology Seminar Series 5/2002 St. Louis, MO – ““Molecular Imaging and Targeted Therapy”
18. Invited Speaker: Molecular Imaging Workshop 6/2002 Helsinki, Finland “Molecular Imaging and Targeted Therapy”
19. Invited Speaker: Joint NASA-NCI Biomolecular Physics and Chemistry Program – Monterey, CA - 7/2002 – “Unconventional Innovative Projects Lessons Learned”
20. Invited Speaker: NCI Unconventional Innovative Projects Program – San Diego, CA - 2/2003 – “Molecular Imaging and Local Drug Delivery With a Novel AvB3-Targeted Nanoparticle Emulsion for Noninvasive Detection and Treatment of Cancer Update”
21. Invited Speaker Seminar- Johns Hopkins Medical School - Department of Radiology 5/2003. Molecular Imaging and Targeted Drug Therapy.
22. Invited Speaker: Small Talk 2003. Molecular Imaging and Targeted Drug Delivery: Emerging Medical Paradigms
23. Invited Speaker: American Chemical Society 2003. New York, NY. September, 2003. Molecular imaging and targeted drug therapy: merging paradigms in medicine.
24. Invited Speaker: IEEE -UFFC. Honolulu, HI. October 2003. Molecular imaging and targeted drug delivery: merging medical paradigms
25. Invited Speaker: Northwestern Echo 2003. Chicago, IL, October 2003. Molecular Imaging.
26. Invited Speaker: AHA-Sunday Sessions. Orlando, FL. November, 2003 Molecular imaging and therapy; new paradigms for 21st century medicine.
27. Invited Speaker Society of Cardiac MRI. Barcelona, Spain February 2004. State of the Art in Molecular Imaging and Targeted Therapeutics.
28. Invited Speaker: 5th Magnetic Microsphere Meeting Scientific and Clinical Applications of Magnetic Carriers. May, 2004. Lyon, France Molecular Imaging

& Targeted Drug Delivery with a Site-specific Nanoparticle Platform Technology
Emerging Opportunities for Non-invasive Diagnosis and Image-augmented
Therapy

29. Invited Speaker: International Symposium on Therapeutic Ultrasound. Kyoto, Japan, September, 2004. Molecular Imaging & Targeted Drug Delivery with a Site-specific Nanoparticle Platform Technology Emerging Opportunities for Non-invasive Diagnosis and Image-augmented Therapy
30. Invited Speaker: 8th Annual Heart Failure Society of America. Toronto, Canada, September 2004. Targeted Imaging and Therapeutics
31. Invited Speaker: Gordon Research Conference. Waterville, Maine. June, 2004. Metals Meddle in Medicine.
32. Invited Speaker. Magnetic Nanoparticle Research Symposium, Baton Rouge, LA, June, 2004. Molecular Imaging & Targeted Drug Delivery with a Site-specific Nanoparticle Platform Technology Emerging Opportunities for Non-invasive Diagnosis and Image-augmented Therapy
33. Invited Speaker: Evanston Hospital/Northwestern University Medical School. March, 2004. Ligand-Directed Nanoparticles in Molecular Medicine: Emerging Opportunities
34. Invited Speaker: Society of Vascular Surgery/NHLBI Joint Workshop March, 2004, Bethesda, MD. Targeted Imaging and Therapeutics.
35. Invited Speaker. ISMRM Workshop on MR in Drug Development, McLean, VA April, 2004 MR Nanoparticles Technology Drug Development for Atherosclerosis
36. Invited Speaker. American Society of Nuclear Cardiology. May, 2004, Bethesda, MD, Combined Therapeutic and Molecular Imaging Agent for Treatment and Monitoring of Plaque Angiogenesis in Atherosclerosis
37. Invited Speaker. American Society of Nuclear Cardiology. May, 2004, Bethesda, MD, Nanotechnology and Molecular Imaging in Atherosclerosis
38. Invited Speaker: Invited Speaker. AHA; Atherosclerosis, Thrombosis, and Vascular Biology. San Francisco, CA May, 2004, Bethesda, MD, Combined Therapeutic and Molecular Imaging Agent for Treatment and Monitoring of Plaque Angiogenesis in Atherosclerosis
39. Invited Speaker. Philips Medical Systems Molecular Imaging Users Group. September, 2004. Saint Louis, MO. Perfluorocarbon nanoparticles: a multimodal platform for targeted therapy and Molecular Imaging.
40. Invited Speaker: University of Virginia Cardiology Grand Rounds. Charlottesville, VA. September, 2004. Emerging Molecular Imaging and Targeted Therapy Opportunities

41. Invited Speaker: University of Nebraska First Annual Biomagnetism Symposium. Lincoln, Nebraska, October, 2004 A Personalized Nanotechnology Approach to Cardiovascular Disease
42. Invited Speaker: WU/Pfizer Retreat on Cardiovascular Disease October, 2004. A Personalized Nanotechnology Approach to Cardiovascular Disease.
43. Invited Speaker: NCI Nanotechnology Conference: Overcoming Barriers to Collaboration. Cleveland, OH, October 2004. Development of Personalized Nanotechnology Approaches to Oncologic Disease
44. Invited Speaker: University of Miami, Department of Medicine and Division of Cardiology Grand Rounds. December, 2004.

triphenylthioalane; SKF-2599; Glior. $C_{15}H_{11}N_2O$; mol wt 259.1. C 73.61%, H 5.92%, N 11.76%, O 6.71%. Prep'd by the reduction of diphenylthiohydantoin with sodium; Biltz, *Synth. Ann.* 391, 218 (1912); with Raney nickel: Whalley *et al.*, *J. Am. Chem. Soc.* 77, 745 (1955); Goodman, U.S. pat. 2,724,852 (1956).

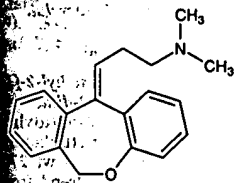


Stout plates from methanol, mp 183° (Goodman); crystals from alc, mp 185.5-186.5° (Biltz). Moderately sol in glacial acetic acid; less sol in alc, ethyl acetate, benzene, chloroform. Practically insol in water, ligroin.

Hydrochloride, $C_{15}H_{11}N_2O \cdot HCl$, dec 205-206°.

THERAP CAT: Anticonvulsant.

3492. Doxepin. 3-Dibenz[b,e]oxepin-11(6H)-ylidene-N,N-dimethyl-1-propanamine; N,N-dimethyldibenz[b,e]oxepin-11(6H)-ylidene-N,N-dimethyl-1-propanamine; 11-(3-dimethylaminopropylidene)-5,6,7,8-tetrahydrodibenz[b,e]oxepin; P-3693A. $C_{20}H_{21}NO$; mol wt 299.38. C 81.68%, H 7.58%, N 5.01%, O 5.73%. Prep'n of mixture of *cis*- and *trans*-isomers: K. Stach, F. Bickelhaupt, *Monatsh.* 93, 896 (1962); F. Bickelhaupt *et al.*, *ibid.* 94, 483 (1963); *Neth. pat. Appl.* 6,407,758; K. Stach, U.S. pat. 3,433,981 (1965, 1969 both to Boehringer Mann.); and separation and activity of isomers: B. M. Bloom, J. R. Hutter, *Belg. pat.* 641,498; *idem.*, U.S. pat. 3,420,851 (1964, 1969 both to Pfizer). Pharmacology: A. Ribbentrop, *W. Schumann, Arzneimittelforsch.* 15, 863 (1965). Metabolism in animals: D. C. Hobbs, *Biochem. Pharmacol.* 18, 141 (1969). Determin in plasma by GC/MS: T. P. Davis *et al.*, *J. Chromatog.* 273, 436 (1983); by HPLC: T. Emm, J. J. Leito, *ibid.* 419, 445 (1987). Clinical study in depression: K. Rickels *et al.*, *Arch. Gen. Psychiat.* 42, 134 (1985). Comparative clinical trial with cimetidine, *q.v.*, in treatment of ulcers: R. K. Shrivastava *et al.*, *Clin. Ther.* 7, 181 (1985). Review of pharmacology and therapeutic efficacy: R. M. Funder *et al.*, *Drugs* 13, 161 (1977).



Oil liq consisting of a mixture of *cis*- and *trans*-isomers. n_D^{20} 1.4467, n_D^{25} 1.4457, n_D^{30} 1.4447. LD₅₀ in mice, rats (mg/kg): *A. Toxicol.* 79, 132 (p.p.); 135, 147 orally (Ribbentrop, Schumann).

Hydrochloride, $C_{20}H_{21}NO \cdot HCl$, *Adapin*, *Aponal*, *Curatin*, *Claron*, *Sinequan*. Crystals, mp 184-186°, 188-189°. (A *trans* mixture of approx 1:5).

Melate, crystals, mp 161-164°, 168-169°.

trans-Form hydrochloride, mp 192-193°.

cis-Form hydrochloride, *cis*-doxepin hydrochloride, P-4599.

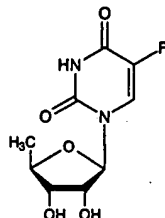
Epilids, mp 209-210.5°.

THERAP CAT: Antidepressant.

THERAP CAT (VET): Antipruritic.

3493. Doxifluridine. 5'-Deoxy-5-fluorouridine; 1-(β -D-ribofuranosyl)-5-fluorouracil; 5'-DFUR; 5'-dFURd; 5'-DFURd; Fluturon; Furtulon. $C_{11}H_{11}FN_2O_5$; mol wt 282.2. C 43.91%, H 3.50%, F 7.72%, N 11.38%, O 32.49%. Purified pyrimidine nucleoside with cytostatic activity. *q.v.* A. F. Cook, U.S. pat. 4,071,680 (1978 to Hoffmann-La Roche); H. Hrebabecky, J. Beranek, *Nucleic Acids Res.* 10, 103 (1978); A. F. Cook *et al.*, *J. Med. Chem.* 22, 1330 (1979). Stereospecific synthesis: J. Kiss *et al.*, *Helv. Chim. Acta* 65, 1522 (1982). Mechanism of action studies: H.-R. Lohmann, A. Maffrè, *Cancer Res.* 42, 2412 (1982); R. D.

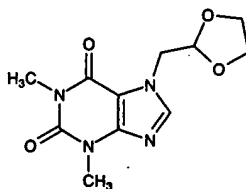
Armstrong *et al.*, *Cancer Chemother. Pharmacol.* 11, 102 (1983). Kinetics and metabolism in humans: J.-P. Sommadossi *et al.*, *Cancer Res.* 43, 930 (1983). Clinical trials in colorectal carcinoma: R. Abele *et al.*, *J. Clin. Oncol.* 1, 750 (1983); S. D. Fossa *et al.*, *Cancer Chemother. Pharmacol.* 15, 161 (1985). Series of articles on animal toxicology: *Yakuri to Chiryō* 13, Suppl. 2, 221-430 (1985); acute toxicity: M. Shimizu *et al.*, *ibid.* 209, C.A. 104, 14673z-14678e (1986). Evaluation of neurotoxicity in humans: M. S. Heier, S. D. Fossa, *Acta Neurol. Scand.* 73, 449 (1986).



Crystals from ethyl acetate, mp 189-190° (Cook). Also reported as crystals from 2-propanol, mp 186-188° (Hrebabecky, Beranek); needles from methanol + ethyl acetate, mp 192-193° (Kiss). pKa 7.4. $[\alpha]_D^{25} +18.4^\circ$ (*c* = 0.419 in water). uv max (in methanol): 268-269 nm (ϵ 8550). LD₅₀ (14 day) in mice or rats (mg/kg): >1000 i.v.; >2000 s.c.; in male, female mice, male, female rats (mg/kg): >5000, >5000, 3471, 3390 orally (Shimizu).

THERAP CAT: Antineoplastic.

3494. Doxofylline. 7-(1,3-Dioxolan-2-ylmethyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione; 7-(1,3-dioxolan-2-ylmethyl)theophylline; 2-(7'-theophyllinylmethyl)-1,3-dioxolane; doxophylline; dioxifylline; ABC-12/3; Ansimar; Maxivent; Ventax. $C_{11}H_{14}N_4O_5$; mol wt 266.26. C 49.62%, H 5.30%, N 21.04%, O 24.04%. Prep'n: U. Avico *et al.*, *Farmaco Ed. Sci.* 17, 73 (1962). Use as bronchodilator: Belg. pat. 868,556; J. S. Franzone, T. Tamietto, U.S. pat. 4,187,308 (1978, 1980 to Istituto Biologico Chemioterapico ABC). Pharmacology: J. S. Franzone *et al.*, *Farmaco Ed. Sci.* 36, 201 (1981). Pharmacodynamics and toxicity in rats: J. S. Franzone *et al.*, *ibid.* 220. HPLC determin in pharmaceutical compositions: C. Badini *et al.*, *Farmaco Ed. Prat.* 37, 320 (1982). Clinical trial in obstructive pneumopathy: C. Bucca *et al.*, *Int. J. Clin. Pharm. Res.* 11, Suppl 1, 101 (1982).

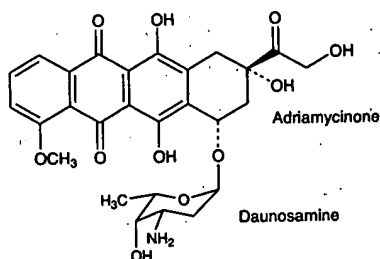


Crystals, mp 144-145.5°. Sol in water, acetone, ethyl acetate, benzene, chloroform, dioxane, hot methanol or hot ethanol. Practically insol in ethyl ether or petr ether. LD₅₀ in mice (mg/kg): 841 orally; 215.6 i.v.; in rats: 1022.4 orally, 445 i.p. (Franzone).

THERAP CAT: Bronchodilator.

3495. Doxorubicin. (8S-*cis*)-10-[(3-Amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacene-dione; 14-hydroxydaunomycin; NSC-123127; FI-106. $C_{27}H_{31}NO_{11}$; mol wt 543.53. C 59.67%, H 5.38%, N 2.58%, O 32.38%. Anthracycline antibiotic isolated from *Streptomyces peucetius* var *caesius*: F. Arcamone *et al.*, S. Afr. pat. 68 02378 and U.S. pat. 3,590,028 (1968 and 1971 to Farmitalia); *idem.*, *Biotechnol. Bioeng.* 11, 1101 (1969). Synthesis of derivs: F. Arcamone *et al.*, Ger. pat. 1,917,874 (1969 to Farmitalia), C.A. 73, 45799r (1970). Structural studies: F. Arcamone *et al.*, *Tetrahedron Letters* 1969, 1007. Synthesis from daunomycin, *q.v.*: *idem.*, *Chim. Ind. (Milan)* 51, 834

(1969); see also: E. M. Acton *et al.*, *J. Med. Chem.* 17, 659 (1974); from 7-deoxydaunomycinone: T. H. Smith *et al.*, U.S. pat. 4,012,448 (1977 to Stanford Res. Inst.). Biochemical comparison with daunomycin: Wang *et al.*, *Proc. Am. Assoc. Cancer Res.* 12, No. 62, 77 (1971). In acid environment doxorubicin breaks up into a water-insoluble aglycone, *adriamycinone* ($C_{21}H_{18}O_5$), and a water-soluble basic, reducing aminosugar, *daunosamine* ($C_6H_{13}NO_3$), 3-amino-2,3,6-trideoxy-L-lyxohexose: A. Di Marco *et al.*, *Cancer Chemother. Rep.* (part 1) 53, 33 (1969). Total synthesis of adriamycinone: F. Suzuki *et al.*, *J. Am. Chem. Soc.* 100, 2272 (1978); regiospecific synthesis: J. S. Swenton, P. W. Reynolds, *ibid.* 6188; of daunosamine: P. M. Wovkulich, M. R. Uskonovic, *Tetrahedron* 41, 3455 (1985). Pharmacokinetic and chemotherapeutic studies: E. Arena *et al.*, *Arzneimittel-Forsch.* 21, 1258 (1971). Purification: E. Oppici *et al.*, Belg. pat. 898,506; *idem*, Brit. pat. Appl. 2,133,005 (both 1984 to Farmitalia). As modulator of immune response in mice: E. Mihlich, M. J. Ehrke, *Transplant. Proc.* 16, 499 (1984). Doxorubicin's cytotoxicity appears to be due to its ability to intercalate with DNA, interact with plasma membranes and take part in oxidation-reduction reactions: T. R. Tritton, G. Yee, *Science* 217, 248 (1982); H. Simpkins *et al.*, *Cancer Res.* 44, 613 (1984); R. S. Youngman, E. F. Elstner, *Arch. Biochem. Biophys.* 231, 424 (1984). In treatment of cancer of the bladder: M. Pavone-Macaluso *et al.*, *Urology* 23, 40 (1984); breast: D. C. Tormey *et al.*, *Am. J. Clin. Oncol.* 7, 231 (1984); prostate: H. Scher *et al.*, *J. Urol.* 131, 1099 (1984). Toxicology: C. Bertazzoli *et al.*, *Experientia* 26, 389 (1970); *idem*, *Toxicol. Appl. Pharmacol.* 21, 287 (1972); R. D. Olson *et al.*, *Life Sci.* 29, 1393 (1981). Review of properties, biosynthesis, fermentation: R. J. White, R. M. Strohshane, *Drugs Pharm. Sci.* 22, 569-594 (1984); of efficacy: H. L. Davis, T. E. Davis, *Cancer Treat. Rep.* 63, 809-815 (1979). Review: R. H. Blum, S. K. Carter, *Ann. Int. Med.* 80, 249-259 (1974); G. Aubel-Sadron, D. Londres-Gagliardi, *Biochimie* 66, 333-352 (1984). Comprehensive description: A. Vigevani, M. J. Williamson, *Anal. Profiles Drug Subs.* 9, 245-274 (1980). Book: *Doxorubicin*, F. Arcamone, Ed. (Academic Press, New York, 1981) 354 pp.



mp 229-231°.

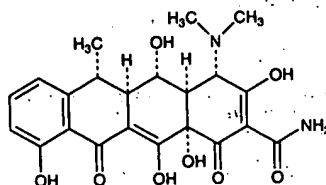
Hydrochloride, $C_{27}H_{29}NO_{11} \cdot HCl$, *Adriacin*, *Adriblastina*, *Adriamycin*. Orange-red colored thin needles, mp 204-205° (dec). $[\alpha]_D^{25} +248^\circ$ ($c = 0.1$ in methanol). Absorption/uv max (methanol): 233, 252, 288, 479, 496, 529 nm. Sol in water, methanol, ac alcohols. Practically insol in acetone, benzene, chloroform, ethyl ether and petroleum ether. Aq solns are yellow-orange at acid pHs, orange-red at neutral pHs and violet-blue at pH > 9. Aq soln unchanged after one month at 5°, but unstable at higher temperatures or at either acid or alkaline pHs. LD₅₀ i.v. in mice: 21.1 mg/kg (Bertazzoli, 1970).

Note: Doxorubicin may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 86.

THERAP CAT: Antineoplastic.

3496. Doxycycline. [4S-(4a,4aa,5a,5aa,6a,12aa)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide monohydrate; α-6-deoxy-5-hydroxy-tetracycline monohydrate; α-6-deoxyoxytetracycline monohydrate; 5-hydroxy-α-6-deoxytetracycline monohydrate; GS-3065; Jenacyclin; Supracycin; Vibramycin. $C_{22}H_{24}N_2O_8 \cdot H_2O$; mol wt 462.46. C 57.14%, H 5.67%, N 6.06%, O 31.14%. Prepnd of

family of 6-deoxytetracyclines: C. R. Stephens *et al.*, *J. Am. Chem. Soc.* 80, 5324 (1958). See also: McCormick, *J. Am. Chem. Soc.* 80, 5324 (1958). U.S. pat. 3,019,260 (1962 to Am. Cyanamid). Preparation and configuration of 6a- and 6b-epimers: M. von Wittenau *et al.*, *J. Am. Chem. Soc.* 84, 2645 (1962); R. Stephens *et al.*, *ibid.* 85, 2643 (1963). Prepnd of α-6-deoxyoxytetracycline: R. K. Blackwood *et al.*, U.S. pat. 3,200,149 (1965 to Pfizer). ¹H-NMR study: M. S. Wittenau, R. K. Blackwood, *J. Org. Chem.* 31, 613 (1966). Biological properties: English, *Proc. Soc. Exp. Biol. Med.* 122, 1107 (1966). Pharmacology: Fabre, *Chemothérapie* 11, 73 (1966); Gibaldi, *ibid.* 12, 265 (1967). Toxicity: hyclate: Goldenthal, *Toxicol. Appl. Pharmacol.* 18, 181 (1971). Clinical trial in prophylaxis of leptospirosis: B. Takafuji *et al.*, *N. Engl. J. Med.* 310, 497 (1984). Review: Edwards in *Pharmacological and Biochemical Properties of Drug Substances* vol. 2, M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1979) pp 305-332.



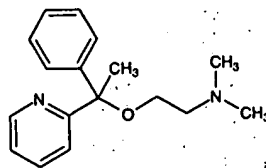
Hydrochloride hemimethanolate hemihydrate, $C_{22}H_{24}N_2O_8 \cdot \frac{1}{2}H_2O \cdot \frac{1}{2}HCl$, *doxycycline hyclate*, *Azudoxal*, *Basado*, *Clinofug*, *Diocimex*, *Doryx*, *Doxatet*, *Doxicrisol*, *Doxchel hyclate*, *Doxylar*, *Doxystem*, *Duradoxal*, *Granadox*, *Hydraxin*, *Mespaflin*, *Nordox*, *Paldomycin*, *Retens*, *Ronaxan*, *Sigadoxin*, *Spanor*, *Tetradox*, *Unacil*, *Vibramycin Hyclate*, *Vibra-Tabs*, *Vibraveineuse*, *Vibravenös*, *Zadorin*. Light yellow, crystalline powder from ethanol + HCl. Chan without melting at about 201°. $[\alpha]_D^{25} -110^\circ$ ($c = 1$ in 0.01N methanolic HCl). uv max (0.01N methanolic HCl): 261, 351 nm (log ε 4.24, 4.12). Sol in water. The alcohol and water of crystallization are lost by drying at 100° under reduced pressure. More active biologically than the corresponding 6b-epimer hydrochloride (Wittenau, 1962). LD₅₀ i.p. in rats: 262 mg/kg (Goldenthal).

Sodium metaphosphate (3:1), $3(C_{22}H_{24}N_2O_8) \cdot NaPO_3 \cdot (HPO_3)_3$, *doxycycline fosfatex*, *Sigacyclat*.

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antibacterial.

3497. Doxylamine. *N,N*-Dimethyl-2-[1-phenyl-1-(2-pyridyl)ethoxy]ethanamine; 2-[α-(2-dimethylaminoethoxy)methylbenzyl]pyridine; phenyl-2-pyridylmethyl-β-*N,N*-dimethylaminoethyl ether; 2-dimethylaminoethoxyphenylmethyl-2-picoline. $C_{17}H_{22}N_2O$; mol wt 270.37. C 75.52%, H 8.20%, N 10.36%, O 5.92%. Prepnd from phenyl-2-pyridylmethylcarbinol and β-*N,N*-dimethylaminoethyl chloride in the presence of sodium in xylene: Sperber *et al.*, *J. Am. Chem. Soc.* 71, 887 (1949). GC determ: H. C. Thompson *et al.*, *J. Chromatog. Sci.* 20, 373 (1982). Pharmacology: antihistaminic activity: B. B. Brown, H. Werner, *J. Clin. Med.* 33, 325 (1948). Hypnotic efficacy: F. Sjöqvist, L. Lasagna, *Clin. Pharmacol. Ther.* 8, 48 (1967). Chronic toxicity study of the succinate: C. D. Jackson, B. Blackwell, *J. Am. Coll. Toxicol.* 12, 1 (1993). Review: T. J. Haley, *Dangerous Prop. Ind. Mater. Rep.* 2, 17 (1982).



Liquid, bp_{0.5} 137-141°. Sol in acids. Slightly volatile, darkens on exposure to light.

Succinate, $C_{17}H_{22}N_2O_4 \cdot C_4H_4O_4$, *Mereprine*, *Alsadorm*, *Capryn succinate*, *Gitalun*, *Hoggar N*, *Sedaplus*, *Unicapryn succinate*, *Gitalun*, *Hoggar N*, *Sedaplus*, *Unicapryn succinate*, *Gitalun*, *Hoggar N*, *Sedaplus*, *Unicapryn succinate*. Crystals, mp 100-104°, sol in water. One gram dissolves

1 ml water, 2 ml alcohol, 2 ml benzene and ether. pH (1% aq mice, rabbits (mg/kg): 470, 250 male rats, female rats (mg/kg): Warner, C.

Note: A combination with py has been marketed as *Bendectin* Prior to 1976. Bendectin also Discussion of Bendectin and th F. Cordero *et al.*, *J. Am. Med. Assoc.* 247, 2234 (1982); L. B. (1983); L. J. Sheffield, R. Bat (1983).

THERAP CAT: Antihistaminic; THERAP CAT (VET): Antihistat

3498. Dragon's Blood. A the fruits of *Daemonorops propi* and probably other species of palms). *Habit.* Sumatra, Bo 55% of a red resin contg ab amorphous dracorresene; 2-3% Isolin of the main coloring ma Haase, *Ber.* 69, 1950 (1936). ments: Olaniyi *et al.*, *J. Che* 179.

Red sticks, pieces, or cak bright-crimson powder; odor ~120° with sublimation of water; sol in alcohol.

USE: For coloring lacquers coloring plasters; in photom metal parts against etching.

3499. Drazoxolon. 3-M and 4,5-isoxazolidone; 4-methyl-5(4H)-isoxazolidone; 4-methyl-5-isoxazolidone; PP. $C_7H_8ClN_2O_2$; mol wt 237. 1492%, N 17.68%, O 13.46% pat. 1,049,103 (1966 to ICI) *Chem. & Ind. (London)* 196 tes: Anderson, Horsgood, S Hydrolysis: Lehtonen *et al.* icology: D. G. Clark, T. F. col. 7, 481 (1969). Review *Plant Growth Regul.* 7, 665.



Yellow crystals, posses benzene, mp 168°. Practic phatic hydrocarbons. Sol (4%), chloroform (about 1:10), stable to dilute acids and LD₅₀ orally in female rat McElligott).

USE: Fungicide.

3500. Drimenin. [9b-Dactahydro-6,6,9a-trin onia $C_{15}H_{22}O_2$; mol wt 226.35. From bark of *D. Appcl*, *Dohr*, *Scientia* 25. Structure and stereoche 1960, 4685. Synthesis: 86, 2044 (1964); Yamagi Nallai-Naini *et al.*, *Tetra*